**Summary:** Hypereosinophilic syndromes in children are rare disorders traditionally characterized by an eosinophil count exceeding 1,500/mm$^3$ on at least 2 occasions or evidence of tissue eosinophilia associated with symptoms and marked blood eosinophilia, lacking any secondary cause (such as infections, allergic disease, chemical-induced eosinophilia, hypoadrenalinism, cancer). Until now there have only been 3 reported cases of pediatric FIP1L1-PDGFRα-positive hypereosinophilic syndromes. We describe a fourth patient, a white 14-year-old boy, the third treated with imatinib.

**Key Words:** hypereosinophilic syndrome, FIP1L1-PDGFRα, myeloproliferative syndrome, childhood, imatinib mesylate

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Recently the International Hypereosinophilic Syndromes Working Group revised both the classic definition and the 2008 WHO classification of hypereosinophilic syndromes (HESs).\(^1\) It is suggested that HESs be defined as: (1) blood eosinophilia $>1,500$/mm$^3$ on at least 2 occasions or evidence of prominent tissue eosinophilia associated with symptoms and marked blood eosinophilia and (2) exclusion of secondary causes of eosinophilia. Included in the new classification are 6 categories of HESs and one of these is the myeloproliferative form that has 2 distinct subcategories: myeloproliferative HESs (not clonal) and chronic eosinophilic leukemia, including FIP1L1-PDGFRα-positive (F/P+).

We report a child who was diagnosed as F/P+ HES and describe the kinetic of response to imatinib.

**CASE REPORT**

A 14-year-old male was referred to our department for pallor, weight loss (3 kg in 2 mo), and left shoulder pain (lasting 2 d). On admission he was in good general condition, weight 47 kg, height 166 cm, BSA 1.47 m$^2$; hepatomegaly (liver 3 cm below the right costal margin), splenomegaly (spleen 8 cm below the left costal margin), and enlarged inguinal (2 cm in maximum diameter) lymph nodes were present. All other lymph nodes were of normal size. The heart and lung findings were within normal limits. Chest x-ray, echocardiography, and electrocardiography were normal.

Blood count showed white blood cells 131,090/mm$^3$ (neutrophils 80,170/mm$^3$, eosinophils 49,000/mm$^3$, lymphocytes 1,030/mm$^3$, monocytes 440/mm$^3$, basophils 450/mm$^3$), Hb 7.7 g/dL, platelets 68,000/mm$^3$; the peripheral blood eosinophil morphology was normal. Serum level of vitamin B$_{12}$ was 1978 pg/mL (normal range, 200 to 800 pg/mL). Routine blood tests, including IgE, were normal. Stool examination for parasites and screening for serum antibodies against CMV, EBV, Toxoplasma gondii, Toxocara canis, Leishmania, Borrelia, Strongyloides stercoralis were negative.

Bone marrow aspiration showed marked hyperplasia of the myeloid lineage, 35% of which consisted of eosinophil precursors, without signs of dysplasia; the myeloid to erythroid ratio was 70:1 with blast percentage <5%. Complete immunophenotype assay, CD4/CD8 ratio, and classic bone marrow cytogenetic analysis were normal. A bone marrow biopsy was not performed. The FIP1L1-PDGFRα rearrangement [fluorescence in situ hybridization (FISH) positive in 97% of bone marrow cells] was observed. WT-1 amplification, studied in peripheral blood, was 122 copies/ABL copies $\times 10^4$ (normal range, 0 to 15). There was no evidence of the following translocations: bcr/abl t(9;22)(q34;q11), BCR-FGFR1 T(8;22)(p11;q11), TEL-PDGFRβ t(5;12)(q33;p13).

Before the molecular diagnosis was determined, the child was treated for 9 days with hydroxycarbamide (500 mg twice daily PO), but eosinophils slightly increased; the complete blood count on day 9 showed white blood cells 177,610/mm$^3$ (neutrophils 98,930/mm$^3$, eosinophils 66,000/mm$^3$, lymphocytes 5,000/mm$^3$, monocytes 6,770/mm$^3$, basophils 910/mm$^3$). After 14 days of therapy with imatinib (100 mg twice daily PO), clinical condition had returned to normal (disappearance of hepatosplenomegaly); blood count had completely normalized after 40 days of imatinib administration (thrombocytopenia last to resolve). FISH performed 45 days after the beginning of treatment was positive in 24% of bone marrow cells; it became completely negative at $+110$ days, whereas the nested/RT-PCR had no signal for the first time in a bone marrow aspiration performed on day $+230$ (Table 1). At the time of writing, 12 months after the diagnosis, the child is asymptomatic with a persistent complete molecular remission.

**MATERIALS AND METHODS**

Two-day cultures without stimulation of bone marrow cells were used for cytogenetics and FISH analysis according to standard procedures. A FISH analysis for detection of the 4q12 was performed using the commercially available FIP1L1-CHIC2-PDGFRα (4q12) deletion, break probe (Kreatech Diagnostics, Amsterdam, the Netherlands). For detection of FIP1L1-PDGFRα fusion transcripts, a nested RT-PCR was performed according to Cools et al.\(^2\) Total RNA was extracted from bone marrow cells using TRIzol reagent (Invitrogen, Carlsbad, CA). First-strand cDNA was synthesized from 1 μg total RNA using Muv reverse transcriptase (Applied Biosystems) with random hexamers according to the manufacturer’s instructions. The fusion was
**TABLE 1.** Molecular and Hematological Monitoring

<table>
<thead>
<tr>
<th>Day</th>
<th>q-PCR WT1 (ex-1-2)</th>
<th>F/P by PCR</th>
<th>F/P by FISH</th>
<th>WBC/mm³</th>
<th>Eosinophil/mm³</th>
<th>Hb (g/dL)</th>
<th>Platelet/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>122</td>
<td>Positive</td>
<td>97.4</td>
<td>177,610</td>
<td>66,000</td>
<td>8.6</td>
<td>36,000</td>
</tr>
<tr>
<td>+ 45</td>
<td>104</td>
<td>Positive</td>
<td>2.34</td>
<td>3,360</td>
<td>40</td>
<td>8.5</td>
<td>68,000</td>
</tr>
<tr>
<td>+ 110</td>
<td>26</td>
<td>Positive</td>
<td>Negative</td>
<td>4,810</td>
<td>160</td>
<td>15.0</td>
<td>149,000</td>
</tr>
<tr>
<td>+ 230</td>
<td>8</td>
<td>Negative</td>
<td>Negative</td>
<td>4,160</td>
<td>80</td>
<td>15.3</td>
<td>139,000</td>
</tr>
<tr>
<td>+ 330</td>
<td>NA</td>
<td>Negative</td>
<td>Negative</td>
<td>9,100</td>
<td>60</td>
<td>14.4</td>
<td>145,000</td>
</tr>
</tbody>
</table>

FISH indicates fluorescence in situ hybridization; NA, not assessed; PCR, polymerase chain reaction; WBC, white blood cells.

analyzed using primers FIP1L1-F4 (5′-actctgtctgatctttctcgtat) and PDGFRα-R1 (5′-aagctccttctctctg) during the first PCR, and primers FIP1L1-F5 (5′-ccagcctagggactgct) and PDGFRα-R2 (5′-gggaccggcttaatccatag) for the second PCR.

**DISCUSSION**

In 2003 Cools et al identified an F/P fusion gene on chromosome 4ql2 in HES patients. The PDGFRα gene encodes the α-chain of the PDGF receptor, a tyrosine kinase receptor class III subtype, which, in the fusion protein, is constitutively activated. The F/P gene can be found, in HESs, in many types of blood cells (eosinophils, neutrophils, basophils, mastocytes, erythrocytes, T lymphocytes, and B lymphocytes); it is unknown why eosinophil proliferation predominates. F/P + patients can be classified, according to International Hypereosinophilic Syndromes Working Group,1 as affected by chronic eosinophilic leukemia or, according to WHO 2008, as affected by a myeloproliferative neoplasm associated with eosinophilia.

F/P + individuals suffer typical organ dysfunction with skin, lungs, digestive tract, nervous system, and heart often involved, even though it seems that endomyocardial fibrosis and mucosal ulcerations are more common.4 Typically the blood count is characterized by leukocytosis, anemia, and thrombocytopenia, tryptase and vitamin B12 are elevated and IgE are normal.2 All these hematological and biochemical aspects (except tryptase, evaluation not performed) were present in our child. He was in good clinical condition, as the aspects (except tryptase, evaluation not performed) were as affected by chronic eosinophilic leukemia, as affected by WHO 2008, as affected by a myeloproliferative neoplasm associated with eosinophilia.

WT1 gene expression is a useful marker for distinguishing a clonal disease from other HESs and its levels, in our patient, decreased along with the concurrent reduction of FIP1L1-PDGFRα transcript (Table 1).

Historically, HESs were treated with steroids, hydroxy-carbamide, and interferon-α but, more recently, imatinib, capable of inhibiting the activated PDGFRα at nanomolar concentrations,9 has become the treatment of choice for F/P + patients. There are only exceptional cases of resistance.10 The doses range from 100 to 400 mg daily11 but in literature there are some reports of response maintained with 100 mg even once a week.12 In the 2 previous pediatric F/P + patients treated with imatinib the dose ranged from 300 mg/m² daily to 400 mg/d (Table 2) but we decided to prescribe imatinib at the most common adult dose (200 mg daily). In one of the largest series11 all 27 adult F/P + patients treated with imatinib had become RT-PCR negative for the FIP1L1-PDGFRα transcripts after 1 to 10 months of therapy. In our case RT-PCR was completely negative after almost 8 months and the boy did not suffer any adverse events. It seems that the response in adult patients is lasting but dependent on treatment, and, when the drug is stopped, the risk of loss of molecular negativity is elevated.11 Our patient, whose brother is HLA compatible, is in perfect general condition with normal quality of life so, with the parents’ agreement, we decided to carry on with imatinib and we plan a slow-dose reduction in the future.

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**REFERENCES**


